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TOWNSEND and TOWNSEND and CREW LLP

By: _____
Lata Olivier

PATENT
Attorney Docket No. 015280-356100US
Client Ref. No. E-201-1998/0-US-06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 3958
PASTAN et al.	Examiner: Zeman, Robert A.
Application No.: 09/673,707	Technology Center/Art Unit: 1645
Filed: January 11, 2001	APPELLANTS' CORRECTED BRIEF UNDER 37 CFR §41.37
For: RECOMBINANT IMMUNOTOXIN DIRECTED AGAINST THE HIV-1 GP120 ENVELOPE GLYCOPROTEIN	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed regarding the above-referenced application, Appellants submit this corrected Brief on Appeal. This corrected Brief is identical to the original Brief submitted November 5, 2007, except for (1) a correction of Section 10, the Evidence Appendix, to state where the evidence submitted by the Applicants was entered into the record, and (2) incorporation of a prior correction of Section 3 of the Appeal Brief to state which claims are under appeal.

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1. REAL PARTY IN INTEREST

The real parties in interest in this proceeding are the Government of the United States, as represented by the Secretary of Health and Human Services, and The Scripps Research Institute.

2. RELATED APPEALS AND INTERFERENCES

To the best of the undersigned's knowledge, there are no related appeals or interferences.

3. STATUS OF CLAIMS

Claims 1-7, 9, 11, 19-24, 52-55, 57, 59-65, 68-75, 77, 79-88, 90-97, 99, and 101-103 are pending and rejected. The rejection of each of these claims is hereby appealed.

Claims 19-24, 59-65, 79-88, 90-97, 99, and 101-103 are withdrawn.

4. STATUS OF AMENDMENTS

All amendments have been entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The invention at issue relates to chimeric molecules, known as immunotoxins, comprising a toxin fused to portions of an antibody known as 3B3. The 3B3 antibody binds to gp120, a 120 kD glycoprotein encoded by the "*env*" ("envelope") gene of human immunodeficiency virus (HIV-1) and present on the surface of cells infected by HIV-1.

The independent claims are presented below as claims chart showing in brackets support in the specification by page and line number for each element:

1. An immunotoxin **[page 11, lines 9-11]** comprising a cytotoxin **[page 11, lines 9-11]** attached to an anti-gp120 antibody **[page 11, lines 7-11]** having the binding specificity to the CD4 binding site of gp120 of 3B3 Fv **[page 2, lines 29-32]** (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2 **[sequence listing]**) and a minimum binding

affinity to gp-120 of 3B3 Fv **[page 2, lines 29-32]** (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2 **[sequence listing]**), wherein said immunotoxin specifically binds to and kills mammalian cells infected with HIV-1 **[page 11, lines 9-11]**.

52. A kit for killing cells that display a gp120 protein, said kit comprising a container containing an immunotoxin **[page 11, lines 9-11]** comprising a cytotoxin **[page 11, lines 9-11]** attached to an anti-gp120 antibody **[page 11, lines 7-11]** having the binding specificity to the CD4 binding site of gp120 of 3B3 Fv **[page 2, lines 29-32]** (SEQ ID NO.:1 **[sequence listing]**) and a minimum binding affinity to gp-120 of 3B3 Fv **[page 2, lines 29-32]** (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2 **[sequence listing]**), wherein said immunotoxin specifically binds to and kills mammalian cells infected with HIV-1 **[page 11, lines 9-11]**.

68. A composition, said composition comprising a pharmaceutically acceptable carrier or excipient; and

an immunotoxin **[page 11, lines 9-11]** comprising a cytotoxin **[page 11, lines 9-11]** attached to an anti-gp120 antibody **[page 11, lines 7-11]** having the binding specificity of 3B3 Fv **[page 2, lines 29-32]** (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2 **[sequence listing]**).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Are the claims obvious under 35 U.S.C. §103 (a) over Matsushita et al., Aids Research Human Retroviruses 6(2):193-203 (1990), in view of Barbas, Proc Natl Acad Sci (USA) 91:3809-3813 (1994), and Pastan, U.S. Patent No. 5,458,878?

B. Are claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 indefinite under 35 U.S.C. §112, second paragraph, for reciting the phrase "which 3B3 Fv consists of a VH chain and a VL chain encoded by SEQ ID NO.:2"?

7. ARGUMENT

I. Introduction

As noted above, the invention at issue relates to chimeric molecules, known as immunotoxins, comprising a toxin fused to antibodies having the binding specificity and affinity of an antibody known as 3B3. *See*, specification, at page 11, lines 7-11. The 3B3 antibody binds to a particular epitope of gp120, a 120 kD glycoprotein encoded by the "*env*" ("envelope") gene of human immunodeficiency virus (HIV-1) and present on the surface of cells infected by HIV-1. *See*, specification, at page 11, lines 12-13.

The Final Action (the "Action") rejects the claims on two grounds, obviousness and indefiniteness. The more important of the rejections is that the claims are as obvious under 35 U.S.C. § 103(a) over Matsushita et al., Aids Research Human Retroviruses 6(2):193-203 (1990) (hereafter, "Matsushita"), in view of Barbas, Proc Natl Acad Sci (USA) 91:3809-3813 (1994) (hereafter "Barbas") and Pastan, U.S. Patent No. 5,458,878 (hereafter, "the '878 Patent"). The Matsushita reference discloses an anti-gp120 antibody, named "0.5β". The 0.5β antibody binds to a portion of gp120 that mutates rapidly and is variable among strains of HIV. In the Matsushita reference, the antibody is coupled to a mutated *Pseudomonas* exotoxin A (hereafter, "PE"). Since 2003, the Examiner has taken the position that, given that Matsushita disclosed an antibody reactive with a number of HIV isolates, it would have been obvious for one of ordinary skill to use the 3B3 antibody in the Matsushita immunotoxin. *See*, June 9, 2003 Office Action at pages 10-11.

As will be shown in more detail below, Applicants rebutted the rejection by introducing evidence that, after the Matsushita reference was published, immunoconjugates directed against gp120 went into clinical trial, and failed. Applicants further presented evidence, in the form of retrospective statements in the open scientific literature, on how persons of skill in the art responded to the disappointing results of the clinical trials. Those statements showed that, in the wake of the trials, persons of skill abandoned pursuing the further development of immunoconjugates against gp120. Applicants observed that persons of skill had before them not only the teachings of Matsushita's 1990 reference, but also the results of the 1994 trials, and that

the motivation to modify the Matsushita immunotoxin found by the Examiner in the reference had been removed by the later clinical trial results.

Until the present Final Rejection, the Examiner simply dismissed the evidence regarding the CD4-PE conjugates on the grounds that they were not analogous to the immunotoxins of the invention.[1] Unfortunately, from 2003 until 2005, the Examiner failed to present any rationale or explanation supporting this conclusion. In a brief note in a 2005 Advisory Action and more fully in an Office Action dated April 2006, the Examiner set forth his rationale, which turned out to be based on the belief that CD4-PE would bind to cells expressing CD4, while the Matsushita immunotoxin would bind only to cells infected with HIV. The Applicants corrected this fundamental misunderstanding of the science with the declaration of a non-inventor who is an expert in the area of targeted toxins such as immunotoxins and who was a co-author on seven pre-clinical studies on CD4-PE. The Declaration explained that CD4-PE does not bind to CD4-expressing cells and that CD4-PE and the Matsushita immunotoxin were in fact analogous in terms of the cells that they bind.

Applicants also provided statements from the open scientific literature as to the belief in the field following the clinical trials involving CD4-PE discussed above. It is unusual for there to be direct statements in the scientific literature as to the conclusion drawn by persons of skill following an event. But, those statements exist in this case, and show that the conclusions actually drawn persons of skill in the art are directly opposed to the conclusions the Examiner thinks persons of skill would have drawn. The examination process normally relies on an examiner's conclusions as to what would have been obvious to a person of skill in the art based on the information at the time. When there is evidence as to what persons of skill actually concluded, the actual conclusions reached by persons of skill should be given precedence over an examiner's conjecture.

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[1] Since CD4 is a cell surface determinant, not an antibody, chimeric molecules comprising CD4 and a toxin are not generally referred to in the art as "immunoconjugates" or "immunotoxins." The Examiner, however, referred to the CD4 conjugates as "immunotoxins" throughout the prosecution, and Dr. FitzGerald referred to them as such in his Declaration to avoid confusion as he quoted portions of the April 13, 2006 Office Action and then responded to the quoted passages. Accordingly, the discussion below will generally refer to chimeric molecules comprising CD4 and a toxin, such as PE, as immunotoxins when summarizing the Examiner's contentions and in presenting Dr. FitzGerald's Declaration, and will otherwise refer to them as "conjugates."

The current Final Action at last acknowledges the factual errors which underlay the rejection for the previous three years. Instead of thoughtfully reconsidering and withdrawing the rejection, however, the Examiner has recharacterized the grounds of the rejection in a way to continue holding that the CD4-PE conjugates and the claimed immunotoxins are not analogous. The Action thereby discounts the effect on persons of skill of the results of the 1994 CD4-PE clinical trials.

In short, the obviousness rejection in this case was originally grounded on a misunderstanding of the science. When the misunderstanding of the science was corrected, the rejection was simply maintained. Further, evidence of what persons of skill in the art actually concluded in light of the information available at the time was ignored in favor of hindsight speculation of what they should have concluded. Applicants respectfully submit that, viewed in light of the science and in view of what persons of skill actually concluded, the obviousness rejection cannot be sustained.

Finally, as will be shown below, the indefiniteness rejection is without merit as the claims cannot be read as contended in the Action. The Board's consideration of these matters and allowance of the claims is therefore respectfully requested.

II. The Obviousness Rejection

Since 2003, the claims have been rejected as obvious over Matsushita in view of Barbas and Pastan. Matsushita et al. discloses an anti-gp120 antibody, named "0.5β" coupled to a toxin comprised of a mutated *Pseudomonas* exotoxin A, or "PE". The current Action maintains the rejection and presents its position as a series of points and responses thereto. To facilitate the Board's review, the individual parts of the rejection are grouped and addressed in logical groups, and the separate points set forth by the Action are then addressed in turn.

A. Any motivation created by the Matsushita immunotoxins was destroyed by the failure of anti-gp120 immunoconjugates in clinical trials

The obviousness rejection rests on the presumption that, at the time the present invention was made, the person of skill would have been motivated to modify the 0.5β-PE

immunotoxin disclosed by Matsushita in 1990 by using antibodies with the binding specificity and affinity of the claimed immunotoxins. As noted above, both Matsushita's 0.5β-PE immunotoxin and the inventors' 3B3 antibody binds to a glycoprotein protein called gp120 that exists in the immunodeficiency virus HIV-1 and in human cells infected with HIV-1. See, e.g., specification, at page 11, lines 9-11.

The rejection's reliance on the Matsushita reference as providing motivation to the person of skill to create the immunotoxins of the present invention is misplaced. In focusing only on Matsushita, it ignores, and therefore fails to give proper weight to, all of the information available to the person of skill at the time the invention was made. That information includes the results of two clinical trials of toxins targeted to the HIV gp120 glycoprotein, and evidence of record as to how persons of skill responded to those results.

Following the publication of the Matsushita reference, two anti-gp120 conjugates went into clinical trials, and both failed. Evidence of the failure of the conjugates in the clinical trials was presented to the Examiner in the form of abstracts of two references: Ramachandran et al., J. Infect Dis 170:1009-13 (1994) (hereafter, "Ramachandran"), and Davey et al., J. Infect Dis 170:1180-8 (1994) (hereafter, "Davey"). The anti-HIV-1 conjugates used in the trials were a CD4-PE40 conjugate and a soluble CD4 ("sCD4")-PE conjugate. CD4 is a cell surface antigen bound by gp120. Thus, the CD4-PE conjugates tested in the clinical trials, like the 3B3-targeted immunotoxins of the invention, bind to the gp120 glycoprotein.[2] Further evidence regarding the clinical trials is set forth in the specification of the application under examination, which, at page 35, line 26 to page 36, line 6, reports that clinical trials of a targeted toxin using a portion of the CD4 molecule containing the gp120 binding site as the targeting moiety demonstrated unexpectedly high toxicity.

Applicants also presented two references from the scientific literature showing how persons of skill responded to the results of the clinical trials: Goldstein et al., J. Infect Dis 181:921-926 (2000) (hereafter, "Goldstein") and a "Perspective" published in the Proceedings of the National Academy of Sciences shortly after the priority date of the subject application,

[2] Both the CD4-PE conjugate and the sCD4-PE conjugate both comprise a form of CD4 and both bind gp120. For convenience of reference, they will be referred to herein collectively as "CD4-PE".

Berger, Moss and Pastan, Proc Natl Acad Sci 95:1151-11513 (1998) (hereafter, "Berger et al.")[3] The Goldstein reference looks back at the state of the art following the disappointing reports set forth in Ramachandran and Davey and states that, in the wake of these reports, the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins had been abandoned. The Berger et al. reference, in turn, states:

> The high hopes from the promising preclinical findings [with respect to the use of CD4-PE40 conjugates] were dashed in the initial Phase I trials with HIV-infected patients [citations omitted]. . . . The significant but reversible hepatoxicity greatly diminished enthusiasm for CD4-PE40 in particular and for Env-targeted toxins in general. The CD4-PE40 clinical program was terminated."

(Emphasis added).[4]

Therefore, while the Matsushita reference, published in 1990, may have suggested the use of immunotoxins against the HIV glycoprotein gp120, by 1994, persons of skill in the art were aware of the Ramachandran and Davey articles reporting the failure in clinical trials of two conjugates targeting gp120. Two separate references in the scientific literature, reviewing how persons of skill interpreted those failures of skill in the art, set forth the effect of those results on the persons of skill in the art. The Goldstein reference states that those results caused practitioners to abandon the use of anti-HIV immunotoxins. The Berger et al. reference states that the results of the clinical trials greatly diminished enthusiasm for *Env*-targeted toxins. The gp120 glycoprotein is encoded by the *env* gene of HIV and is therefore encompassed by the Berger et al. statement quoted above. (*See, e.g.*, Berger, at page 11511, paragraph bridging left and right hand columns: "The Env-binding moieties used have included the extracellular regions of CD4 as well as Fab regions of anti-Env antibodies (directed at either the external subunit gp120 or the transmembrane subunit gp41).") In other words, persons of skill as of the 1998

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[3] To avoid the possibility of confusion, references herein to Berger et al. refer to this 1998 PNAS publication and not to two other publications by Dr. Berger whose abstracts are presented as Exhibits to the FitzGerald Declaration.

[4] During prosecution, the Examiner dismissed the Goldstein reference as irrelevant since it was published after the priority date. Applicants explained that it was cited only for its retrospective statements as to what persons of skill thought in the wake of the CD4-PE clinical trials. See, Amendment dated September 19, 2005, at pages 20-

priority date of the application would have before them not only the Matsushita reference relied on by the rejection, but also the results of the clinical trials, which two references tell us caused persons of skill to abandon the approach of using anti-gp120 antibodies to target toxins to HIV-infected cells. Accordingly, following the 1994 clinical trial results, persons of skill no longer had motivation to modify Matsushita to develop anti-gp120 immunotoxins, as shown by the Berger and Goldstein references as well as by the gap of years between those trials and the present invention.

The present invention stems in part from the realization by the present inventors that there had been a further change in the treatment landscape for HIV. New classes of anti-HIV drugs, such as protease inhibitors, had become available, resulting in the treatment regimens known as "highly active anti-retroviral therapy", or "HAART". The inventors realized that, while toxins targeted to gp120 had failed as a first line therapy, as contemplated before the failure of the CD4-PE trials, toxins targeted to gp120 could be used to kill cells serving as reservoirs of HIV in persons in whom HIV loads had already been reduced by HAART. *See*, specification, at page 11, lines 13-18; Berger et al., at page 11511, first paragraph. This was a new use unforeseen at the time of Matsushita and the CD4-PE trials. Thus, while development of toxins targeted to gp120 had been abandoned following the 1994 CD4-PE trials, the inventors realized HAART had changed the landscape. Hence, they developed the compositions encompassed by the claims under rejection as a solution to the long felt for additional HIV treatment strategies, and two of them then served as co-authors on the Berger paper explaining that change in the landscape to the scientific community in the Berger reference.

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21. The Berger reference was also submitted with the September 2005 Amendment. As discussed in the text, it does not appear that the Examiner has ever addressed or considered the Berger reference.

B. The Ramachandran And Davey Conjugates And The Immunotoxins Of The Invention Are Analogous

1. The Ramachandran And Davey Conjugates And The Immunotoxins Of The Invention Bind and Kill The Same Target Cells

The Office Action dated April 13, 2006 (the "April 2006 Action") states that the CD4-PE conjugates of Ramachandran and Davey that failed in clinical trials are not analogous to the immunotoxins of the claimed invention "since they target different cellular components." April 2006 Action, at page 6. The Action further stated that "[t]he immunotoxins of the instant invention . . . target cells expressing gp120 on their surface (i.e., infected cells) whereas the CD4-PE40 immunotoxin of Ramachandran et al. target any cell expressing CD4. Hence any 'results' based on the application of CD4-PE40 immunotoxin would not have any bearing on the perceived efficacy of immunotoxin based on the combination of the cited references. The same is true for the sCD[4]-PE immunotoxin disclosed by Davey et al." *Id.*

In response to the Examiner's explanation, Applicants submitted a Declaration of Dr. David FitzGerald (hereafter, the "Declaration"). Dr. FitzGerald is not an inventor of the present invention. He is, however, an expert in the field of targeting toxins to cells, having worked in the field since 1982. Declaration, at ¶5. Moreover, Dr. FitzGerald is specifically knowledgeable about the attempts to develop targeted toxins of CD4-PE for use as therapeutic agents for HIV-1, as reflected by the fact that he was a co-author of the first study on the use of a CD4-PE conjugate to kill HIV-1 infected cells (Declaration, at ¶¶5-6), as well as six additional publications on the pre-clinical development of these conjugates (Declaration, at ¶7).

Dr. FitzGerald was provided with the position set forth in the April 2006 Action. He stated in his Declaration that the Action's position is factually incorrect and would have been known to be incorrect by a person of skill in the art as of the June 1998 filing date of the priority provisional application. Declaration, at ¶14. He stated that CD4 is a cell surface marker on the surface of certain cell types, such as B cells and macrophages, that is bound by the gp120 protein of HIV-1, and that CD4 does not bind to itself. *Id.* He stated that neither the CD4-PE40

immunotoxin of Ramachandran nor the sCD4-PE immunotoxin of Davey would bind cells expressing CD4, as stated by the Action. *Id.*

Dr. FitzGerald further stated that the CD4-PE40 immunotoxin of Ramachandran and the CD4-PE immunotoxin of Davey were intended to bind were cells infected by HIV-1, which express gp120 on their surface and that the immunotoxins recited in the claims under examination have the binding affinity of the 3B3 Fv, which binds to the gp120 protein. Thus, he stated that both (i) the CD4-PE40 immunotoxin of Ramachandran and the sCD4-PE immunotoxin of Davey, and (ii) the immunotoxins of the present invention, bind to cells expressing gp120, and not to cells expressing CD4. He stated that he and others in the art would therefore consider them to be analogous in terms of the cells they were intended to bind. Declaration, at ¶ 15.

2. The Final Action Shifts The Grounds of The Rejection, But The New Ground Does Not Cure the Defects In Analysis

In the face of Dr. FitzGerald's Declaration, the present Final Action acknowledges that CD4-PE conjugates will bind to cells expressing gp120. Action, at page 5. Thus, the Final Action acknowledges that the Declaration overcomes the only rationale previously set forth to support the Examiner's assertions that that the Ramachandran and Davey CD4-PE conjugates are not analogous to the immunotoxins of the present invention . The Final Action, however, now asserts that the rejection was actually supported by a different rationale, and that under this new rationale, the CD4-PE conjugates are not analogous to the immunotoxins of the present invention. The Final Action then concludes that the CD4-PE 1994 clinical trial results are therefore less relevant than the *in vitro* results reported in the 1990 Matsushita reference. According to the Action:

> "the rejection was maintained based on the fact that Matsushita's immunotoxin was shown to have efficacy. Since Matsushita's immunotoxin [] comprises the same components (i.e., a PE toxin and an anti-gp120 antibody) its demonstrated efficacy would have a greater impact on the skilled artisan than the failure of a[n] immunotoxin comprising differing components (i.e., a PE toxin and CD4)."

Final Action, at page 5.

Thus, the Final Action's rejection of the CD4-PE immunoconjugates as analogous to the immunotoxins of the invention is no longer that they do not bind to the same cells, as previously asserted, but that they are not comprised of the "same components." This rationale, however, cannot support the rejection, for at least four reasons.

(a) "Same" vs. Different "Components "

First, the Action fails to set forth any differences that might exist between CD4 and an anti-gp120 antibody as "components" that would lead persons of skill to disregard the failure of the CD4-PE immunoconjugates in the 1994 human clinical trials in favor of the *in vitro* experiments reported by Matsushita in 1990. For example, the Final Action fails to present any argument or evidence that there are any structural or functional differences between CD4 and the 0.5β antibody of Matsushita which would have led the person of skill at the time the invention was made to have expected that the Matsushita immunotoxins would have a better or different result in human clinical trials than did the CD4-PE immunoconjugates. Applicants respectfully note that it is the Examiner's burden to present evidence to overcome the presumption that an applicant is entitled to a patent unless the Examiner can demonstrate to the contrary. And, as will be shown below, the response of persons of skill in the art to the clinical trials was exactly to the contrary: they discontinued the development of anti-*Env* toxins, showing that they considered them analogous to one another.

(b) Effect of Efficacy of Matsushita Immunotoxins In Motivating Practitioners

Second, as noted, the Action cites as support for its assertion that the "demonstrated efficacy" of the Matsushita immunotoxin "would have a greater impact on the skilled artisan than the failure of a[n] immunotoxin comprising different components." Action, at page 5. The assertion that the Matsushita immunotoxin had efficacy that would have motivated the practitioner to modify it despite the results of the 1994 clinical trials however, was contradicted by Dr. FitzGerald in his Declaration. The "efficacy" that Matsushita discloses is

that "toxin-conjugated anti-gp120 monoclonal antibody selectively killed HIV-infected cells in vitro." Matsushita, at page 199, second paragraph. Dr. FitzGerald stated that he therefore considered the efficacy disclosed in Matsushita to be similar to that of the *in vitro* efficacy of CD4-PE in killing HIV-1 infected cells disclosed in his own publication in Nature two years earlier (Declaration, at ¶19, item (iii)). Dr. FitzGerald stated that this *in vitro* efficacy would not by itself give persons of skill any reason to expect a different result with the 0.5β antibody of Matsushita than that found in clinical trials of CD4-PE toxins. *Id.*

The Final Action neither specifically acknowledges Dr. FitzGerald's statements regarding these points, nor shows that they are incorrect or unworthy of credence. It merely ignores the declaration and repeats the unsupported assertions about the alleged motivation provided by the efficacy of the Matsushita immunotoxins as if Dr. FitzGerald's statements had not been presented. Proper examination practice, however, requires that declaration testimony by a person of skill be considered and that rejections be reconsidered in light of the all the evidence, including that presented by declaration.

(c) The Evidence Shows That The Results Of The Clinical Trials Caused Persons Of Skill To Abandon The Approach of Anti-HIV Immunotoxins

Third, the evidence of record contradicts the Examiner's position. Applicants presented two publications published in the open scientific literature stating the reaction of persons of skill to the 1994 failed clinical trials. The Berger et al. "Perspective" published in the Proceedings of the National Academy of Sciences ("PNAS") characterized the effect of the failure of the CD4-PE40 immunoconjugates on persons of skill as follows: "[t]he significant but reversible hepatoxicity greatly diminished enthusiasm for CD4-PE40 in particular and for *Env*-targeted toxins in general." (Emphasis added). Since gp120 is a protein encoded by *Env*, the Berger et al. statement that practitioners were discouraged by the clinical trial results from using gp-120-targeted toxins includes the gp120-targeting Matsushita immunotoxin. The Final Action neither acknowledges the Berger et al. statement, nor explains why the statement is either incorrect or not entitled to weight and consideration. Indeed, there is no evidence on the record that the Examiner gave the Berger reference any consideration.

The authors of the Berger et al. PNAS Perspective are Dr. Pastan of the National Cancer Institute, Dr. Bernard Moss, chief of the Laboratory of Viral Diseases of the National Institute of Allergy and Infectious Diseases ("NIAID"; the NIAID is the Government's lead agency in the fight against HIV/AIDS), and Dr. Berger, also of the NIAID. Moreover, as shown under the title and authors, the Perspective was edited by Dr. Anthony S. Fauci. Dr. Fauci has been the Director of the NIAID since 1984 and according to his biography on the NIAID website, has served as a key advisor to the White House and to the Department of Health and Human Services on developments regarding HIV. According to the website of the National Academy of Sciences, Dr. Pastan has been a member of the Academy since 1982, Dr, Moss has been a member since 1987, and Dr. Fauci has been a member since 1992.[5]

Thus, the Perspective was authored by two National Academy members and edited by a third, who is also the head of the nation's lead agency for combating HIV. It was written for, and published in, a major scientific journal almost immediately after the priority date of the subject application, and sets forth the characterization by these prominent scientists of the effect the failure of the CD4-PE clinical trials had on the efforts of persons in the field. That effect, according to their characterization virtually contemporaneous with the priority date of the present invention, was that the trials discouraged persons in the field from further development of *Env*-targeted toxins, such as the Matsushita anti-gp120 immunotoxin. This characterization was echoed by the Goldstein reference, which states, at page 921, right hand column, bottom paragraph, that in the wake of the reports of the 1994 clinical trial results, the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins was abandoned.[6]

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[5] MPEP §2144.03 sets forth the conditions under which an Examiner can take official notice of information. The MPEP cites *In re Ahlert*, 424 F.2 1088, 165 USPQ 418 (CCPA 1970) as stating that Examiners' may take notice of facts beyond the record when the facts are "capable of such instant and unquestionable demonstration as to defy dispute." See, MPEP at page 2100-134. By parity of reasoning, the Board should take official notice of the facts set forth above, which are immediately ascertainable and not capable of dispute. The facts regarding the National Academy membership of Drs. Pastan, Moss, and Fauci are immediately ascertainable from the National Academy of Sciences website at http://www.nasonline.org/site/Dir?sid=1011&view=basic&pg=srch. The facts of the NIAID's lead role in the efforts of the U.S. Government to attack HIV/AIDS, of Dr. Fauci's position as Director of the NIAID, and of Dr. Fauci's role as a key advisor to the Government on developments regarding HIV are likewise immediately ascertainable and not capable of dispute. They can be found on the NIAID website, at http://www3.niaid.nih.gov/about/directors/biography/director.htm.

[6] Although the Berger and Goldstein articles appeared after the priority date of the application, the statements for which they are presented are characterizations of the state of the art after the CD4-PE40 trials and

Once again, the Final Action neither acknowledges the evidence presented by the Applicants, nor shows why it is either incorrect or unworthy of credence. The almost contemporaneous characterization in the scientific literature by the prominent authors of the Berger reference of the response of persons of skill to the results of the clinical trials, and the similar characterization made in the scientific literature two years later by the Goldstein authors, are evidence of how persons of skill actually responded to the 1994 clinical trial results. Applicants respectfully submit that this evidence of how persons of skill actually responded should control over the hindsight, and unsupported, view of the Examiner as to how persons of skill should have responded.

Finally, Applicants respectfully observe that both Berger and Goldstein are cited by the Applicants for their statements that, in the wake of the Ramachandran and Davey reports, the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins was abandoned. Both statements are retrospective characterizations what people of skill in the art thought following the publication of those reports, and neither relies on information that was not available at the time the invention was made.

(d) The Final Action's Speculation As To Why The Ramachandran and Davey Conjugates Had Hepatotoxicity Does Not Affect Their Nature As Analogous To The Matsushita Immunotoxins

The Ramachandran and Davey CD4-PE immunoconjugates failed in clinical trials because they caused hepatotoxicity which was not seen in the pre-clinical testing. The hepatotoxicity limited the doses that could be administered to levels below that which had been shown to be effective in killing HIV-1 infected cells in vitro. *See, e.g.*, Berger, *supra*, at page 11511, right hand column, bottom paragraph. In the April 2006 Office Action, the Examiner presented the following argument:

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prior to publication of the articles. These retrospective statements do not introduce or rely on information that was not available prior to the priority date. Accordingly, as Applicants have previously argued, both references should be considered.

> "since the CD4-PE immunotoxin would bind to any cell expressing CD4 on its surface, the hepato[to]xicity would logically be the result of said immunotoxin binding to healthy cells thereby disrupting some cellular or endocrine cascade present in man but not the mouse."

April 13, 2006 Action, at pages 6-7, bridging paragraph (emphasis added). Thus, the April 2006 Action expressly attributed the hepatotoxicity of the CD4-PE immunoconjugates to the alleged tendency of CD4 to bind to healthy CD4-expressing cells. In turn, the alleged tendency to bind healthy cells was cited as support for the Action's conclusion that the CD4-PE immunoconjugates were not analogous to the immunotoxins of the invention, which the Action considered not to have that tendency.

As noted in Section B. 1, above, Dr. FitzGerald's Declaration showed that the Action's premise that CD4 would bind to healthy cells was erroneous. Dr. FitzGerald declared that, to the contrary, CD4 would bind to cells expressing the HIV glycoprotein gp120, and that both CD4-PE and the Matsushita immunotoxins would bind the same cells.

In response, the Final Action rewrites the history of the rejection to assert that, contrary to the express statement in the April 2006 Action quoted above,

> "the Examiner did not state that the hepato[to]oxicity was due to the direct binding of the CD4-PE toxin to hepatocytes but that said toxin 'disrupted some cellular or endocrine cascade present in man but not in the mouse."

Final Action, at page 5. This statement is only true to the extent that the April 2006 Action stated that the toxicity was due to the direct binding of CD4-PE to "healthy cells," not to "hepatocytes" per se. It is also true, however, that the only reason the April 2006 Action gave for the hepatotoxicity seen in the CD4-PE clinical trials was that CD4-PE would bind to healthy cells and thereby initiate a cellular or endocrine cascade. It is also true that the April 2006 Action held that the Matsushita immunotoxins and the CD4-PE conjugates were not analogous precisely because of its premise that the Matsushita immunotoxins, in contrast to the CD4-PE conjugates, would not bind to healthy cells. Since Dr. FitzGerald's Declaration showed that the premise that CD4 would bind to healthy cells was completely wrong, and that both CD4-PE and the Matsushita immunotoxins would bind the same cells, the Declaration also destroyed the

premise on which the Action contended that the Matsushita immunotoxins and the CD4-PE conjugates were not analogous.

The Final Action now tries to have it both ways. On the one hand, the Final Action denies that the premise that CD4-PE would bind to healthy cells was the basis of the prior rejection. On the other hand, it still tries to assert that the hepatotoxicity of the CD4-PE conjugates was due to an alleged "cellular or endocrine cascade present in man but not in the mouse". This new basis for rejection suffers from several flaws, each of them fatal to the Action's assertion. First, absent the alleged difference of the two agents in binding healthy cells which underlay the April 2006 Action, there is no basis on which the current Final Action can explain why the person of skill would not have expected the same hepatotoxicity from the use of the Matsushita immunotoxins as was seen in the CD4-PE clinical trials. The lack of a basis for differentiating the two alone supports the conclusion that the CD4-PE conjugates and the Matsushita immunotoxins are analogous.

Second, the Examiner's assertion that there is "some cellular or endocrine cascade present in man but not in the mouse" is unsupported speculation cloaked in scientific-sounding language. The Examiner presents no evidence that such a cascade exists nor, that if one does, that it is the mechanism by which the CD4-PE conjugates had toxicity. Further, the Examiner does not show that, even if such a cascade does exist, one of skill would have expected the cascade to be absent with respect to the Matsushita immunotoxins, which persons of skill would recognize as binding to the same cells as the CD4-PE conjugates. As noted above, the only basis which the Examiner asserted for concluding that the hepatotoxicity of CD4-PE and the Matsushita immunotoxins would be different was that they allegedly bound to different cells, which was shown to be untrue by Dr. FitzGerald's Declaration.

Further, therapeutic agents do not proceed into human clinical trials based on pre-clinical studies in only one species. As set forth in the specification, at pages 35-36, bridging paragraph, pre-clinical studies on CD4-PE showed that it was "very well tolerated by monkeys" which could have relatively high doses "administered daily for 10 days without serious toxicity." This was another reason the very high toxicity seen in the human clinical trials was such a surprise. *Id.* Thus, the "cellular or endocrine cascade" hypothesized by the Examiner must

under his premise exist in man but not in non-human primates. Once again, however, the Examiner has not only failed to set forth any evidence that such a cascade exists, but also failed to set forth any evidence that, if the cascade did exist, the person of skill would have a reason to expect that the cascade would be activated by CD4-PE but not by the Matsushita immunotoxin.

Accordingly, even assuming that the revision of the ground of the rejection in the present Office Action has merit, the Examiner's speculation that some cascade is responsible for the hepatotoxicity of the CD4-PE conjugates does not. It is not only unsupported, but even if true, would fail to support the thesis that the CD4-PE conjugates are not analogous to the Matsushita immunotoxin.

C. The Final Action's Points Do Not Overcome The Showing Of Lack of Motivation To Modify The Matsushita Immunotoxins

On pages 5-6 of the Final Action, the Examiner sets forth responses to various points into which he has divided the asserted grounds for holding the claims obvious over the Applicants rebuttals. While the substance of most of these points has been addressed in the discussions above, for the convenience of the Board in conducting its review , the arguments regarding each "point" is summarized below.[7]

Point 2.

Point 2 sets forth the Examiner's hypothesis that some cellular or endocrine cascade in humans but not mice was responsible for the hepatotoxicity seen in the CD4-PE clinical trials. As set forth in the preceding section, this hypothesis is unsupported speculation that ignores the fact that the CD4-PE conjugates were also tested in non-human primates. Further, even assuming such a cascade was indeed the explanation behind the hepatotoxicity, it would fail to explain why a person of skill would not expect the same cascade, and resulting hepatoxicity, to result from the use of the Matsushita immunotoxin, which target and bind to the same cells as do the CD4-PE conjugates. And, as shown by the Berger and Goldstein references,

[7] Point 1 on page 5 of the Final Action does not need to be addressed since it is the Examiner's acknowledgement that CD4-PE binds cells expressing gp120, not cells expressing CD4, as he had previously contended.

the expectation in the art was that the same problems would arise, which is why the persons of skill discontinued developing anti-gp120 immunotoxins until the work embodied in the present application.

Point 3.

Point 3 argues that persons of skill would be motivated by the efficacy of the Matsushita immunotoxin to modify it to create the current invention, and would be undeterred by the failure of the CD4-PE conjugates because the claimed immunotoxins, unlike the CD4-PE conjugates, has the same components as the Matsushita immunotoxin. As set forth above, the efficacy of the Matsushita immunotoxin was in *in vitro* killing of HIV-infected cells, and is therefore the same efficacy as seen with CD4-PE. Further, it fails to explain why a person of skill would not expect the Matsushita immunotoxin to exhibit the hepatotoxicity seen with the CD4-PE conjugates, which target and bind to the same cells. Second, the argument that the "components" are not the same fails to identify any structural or functional differences between CD4 and an anti-gp120 antibody that would cause the person of skill to expect a difference in hepatotoxicity of the immunotoxin compared to that exhibited by the CD4-PE conjugates.

Third, the argument that the efficacy of the Matsushita immunotoxin would have a greater impact on practitioners than the failure of an immunotoxin with differing components ignores the evidence that exactly the reverse was true. The Berger and Goldstein references state that persons of skill in the art responded to the failure of the CD4-PE conjugates in clinical trials by abandoning the approach of *Env*-directed toxins. They also show that, despite the Examiner's continual refusal to concede that the CD4-PE conjugates and the Matsushita immunotoxin are analogous, persons of skill in the art considered *Env*-directed toxins to be analogous to the CD4-PE constructs. As noted above, the Final Action does not acknowledge the Applicants' contentions regarding the Berger reference or the Goldstein reference, and does not show that the characterizations of the response of persons of skill in the art to the clinical trials set forth in those references is either incorrect or false. The Applicants respectfully maintain that, where there is evidence of record as to how persons of skill actually responded to a clinical result, that

evidence must govern over an examiner's after the fact speculation as to how he thinks artisans should have responded.

Point 4.

Point 4 of the Final Action asserts that the type-specificity of Matsushita's antibody would provide motivation for the artisan to substitute it with the more broadly applicable antibody used in the claimed immunotoxins. This assertion again relies on the assumption that the CD4-PE conjugates are not analogous to the Matsushita immunotoxin, and thus would not have affected the motivation of the practitioner to continue the development of anti-gp120 antibodies. As stated above, however, the Berger and Goldstein references state that persons of skill in the art responded to the failure of the CD4-PE conjugates in clinical trials by abandoning the approach of *Env*-directed toxins. The references also show that, despite the Examiner's continual refusal to concede that the CD4-PE conjugates and the Matsushita immunotoxin are analogous, persons of skill in the art considered *Env*-directed toxins to be analogous to the CD4-PE constructs.

Point 5.

The April 2006 Action stated at page 6: "since the CD4-PE40 immunotoxin would bind to any cell expressing CD4 on its surface, the hepatotoxicity would logically be the result of said immunotoxin binding to healthy cells thereby disrupting some cellular or endocrine cascade present in man but not the mouse." In his Declaration, Dr. FitzGerald corrected the serious factual errors in the Action's position, including the following: (i) CD4 does not bind to itself, (ii) CD4-PE40 would not bind to any cell expressing CD4, and (iii) hepatocytes do not express CD4. Declaration, at ¶¶17-18. He also noted that the Matsushita immunotoxin and the CD4-PE40 were analogous in terms of the cells that they bind. Declaration, at ¶15. He therefore observed that there would be no reason to think that the hepatotoxicity observed in trials of CD4-PE immunotoxins would not also be found with respect to toxins targeted by the antibody of Matsushita. Declaration, at ¶19(ii). Point 5 of the Final Action responds to this portion of Dr. FitzGerald's Declaration with three statements, each of which will be considered in turn. .

First, the Action states that, "given that the components" (the targeting portion) "of the two immunotoxins are different, one cannot predict whether or not they would have the same effects *in vivo*." Final Action, at page 5. The Examiner has not, however, identified any structural or functional differences between the Matsushita antibody and CD4 which would lead one to expect a different response when the two are administered *in vivo*. And, the evidence of record is to the contrary. Both the Berger and the Goldstein references state that, in the wake of the 1994 clinical trial reports, the persons in the art, who were the best positioned to determine whether the clinical trial results could be extrapolated to other targeting moieties, discontinued developing *Env*-targeted toxins. Thus, persons of skill predicted that other anti-gp120 toxins would suffer from the same *in vivo* effect as that seen in the CD4-PE trials.

Next, the Action states at page 5 that, "as Applicant[s have] provided no proof substantiating their speculative assertion, it is deemed non-persuasive." This statement is best understood in context. As noted, Dr. FitzGerald was responding to an argument in the April 2006 Action that CD4-PE would bind to cells expressing CD4 and to hepatocytes, thereby initiating some unknown cascade, resulting in hepatoxicity. Dr. FitzGerald's Declaration established that each of the Action's contentions was based on a serious misunderstanding of the science.

Dr. FitzGerald's statement that there would be no reason to think that the hepatotoxicity observed in trials of CD4-PE immunotoxins would not also be found with respect to toxins targeted by the antibody of Matsushita, Declaration, at ¶19(ii), is therefore not an unsupported assertion, as characterized by the Action, but a logical conclusion based on the correction of the scientific errors in the April 2006 Action's hypothesis. Dr. FitzGerald has been a researcher on targeting toxins to cells since 1982 (Declaration, at ¶5), and is a co-author of 7 papers in the scientific literature specifically on CD4-PE (*id.*, at ¶¶6 and 7). Accordingly, both his factual statements and his analysis are supported by deep familiarity with the attempts in the art to use immunotoxins and CD4-PE as therapeutic agents.

Finally, point 5 states that the basis of the rejection is whether the skilled artisan would have been motivated by the efficacy of the Matsushita immunotoxin to modify it, not whether the resulting immunotoxin would be successful in clinical trials. The Action seems to

take the position that practitioners in the art were engaged in abstract research to develop immunotoxins that would have no real world use. Contrary to the Action's premise, however, practitioners were trying to develop agents that would be useful in reducing HIV infection in patients with HIV. The Matsushita reference, for example, states that the killing effects seen by their immunotoxins *in vitro* suggested the "possible use of the immunotoxins to eliminate selectively HIV-producing cells in vivo." Matsushita, at page 199, bottom paragraph. As noted in Berger, however, the disappointing results of the CD4-PE trials caused greatly reduced enthusiasm for *Env*-targeted toxins in general. Berger, at pages 11511-11512, bridging paragraph. Since the Matsushita immunotoxin is an anti-gp120 toxin, and since gp120 is encoded by the Env gene of HIV, this statement evidences that the high hopes for anti-Env toxins like those of Matsushita immunotoxin were dashed by the CD4-PE results.

Point 6.

In point 6, the Action repeats its contention that the efficacy of the Matsushita immunotoxin, which has the same components as the immunotoxins of the invention, would have more impact on the practitioner than the failure of the CD4-PE conjugates. Action, at pages 5-6, bridging paragraph. As observed above, in Section B.2. (b), the assertion that the Matsushita immunotoxin had efficacy that would have motivated the practitioner to modify it despite the results of the 1994 clinical trials as contradicted by Dr. FitzGerald in his Declaration. Similarly, as set forth in Section I.B.2.(a), the Final Action fails to present any argument or evidence that there are any differences between CD4 and the 0.5β antibody of Matsushita which would have led the person of skill at the time the invention was made to have expected that the Matsushita immunotoxins would have a better or different result in human clinical trials than did the CD4-PE immunoconjugates.

The Action discounts Dr. FitzGerald 's testimony by stating that, by his "logic, a failure of any given treatment modality would forever dissuade any study of not only that treatment modality, but any other that is similar to it. This is not the methodology that used by the artisans in the biomedical arts." Action, at page 6. This sets up a straw argument. When one treatment modality fails, artisans do try similar treatment modalities, when there is some rational

basis on which to think the results might be different. By the same token, when one treatment modality fails, they will not continue wasting resources on a failed approach in the absence of a rational basis to expect a different result.

As shown above, the CD4-PE conjugates and the Matsushita immunotoxin were considered analogous by persons of skill. Moreover, as evidenced by the Berger reference, practitioners were discouraged from further development of *Env*-targeted toxins, such as the Matsushita anti-gp120 immunotoxin. This characterization was echoed by the Goldstein reference, which states, at page 921, right hand column, bottom paragraph, that in the wake of the reports of the 1994 clinical trial results, the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins was abandoned. The Action's reliance on the position that the Matsushita immunotoxins would not have been considered analogous to the CD4-PE conjugates is not only based on scientific fallacy, but is also contrary to the evidence of record.

Point 7.

In point 7, the Examiner acknowledges that there remains a need for AIDS treatments, and states that this need would motivate practitioners to modify the Matsushita immunotoxin. The Examiner dismissed the evidence presented by the Applicants that the Matsushita immunotoxin had never in fact been brought into clinical trials (see, FitzGerald Declaration at ¶20) because the artisan would have been motivated to fine tune it. Action, at page 6.

The contention that artisans would have been motivated to "fine tune" the Matsushita antibody ignores, however, evidence that was already of record in this proceeding. The consideration of long felt need as a secondary consideration of non-obviousness, as set forth by the Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), was brought to the Examiner's attention in Applicants' Amendment dated September 19, 2005. Applicants there presented PubMed searches for references on anti-gp120 immunotoxins and on anti-HIV immunotoxins that were dated between the publication of Matsushita in 1990 and the priority date of the present application in 1998. The searches uncovered no references that appeared

from their titles to relate to the making or testing of anti-gp120 immunotoxins. In fact, from the titles, the Matsushita reference was the only reference that that actually appeared to relate to making an anti-gp120 immunotoxin. For the Board's convenience, the searches presented in 2005 are attached as Exhibits.

In light of this evidence, Applicants submitted that the fact that there did not appear to be a single publication on the development of an anti-gp120 immunotoxin in the approximately eight years between the publication of Matsushita and the priority date of the present application, despite the long felt need to develop anti-HIV therapeutics and the failure of CD4-PE40 immunotoxin, was clear evidence that persons of skill were not motivated by Matsushita, alone or in combination with Barbas and Pastan, to develop an anti-gp120 immunotoxin.

The Examiner has never addressed this evidence. In the Advisory Action of October 12, 2005, he simply maintained that the Matsushita immunotoxin met the long felt need for AIDS treatments, without explanation or analysis of the search results. Advisory Action, at page 6. The present Action does not maintain that Matsushita met the long felt need for a therapeutic, but argues that it provided motivation while ignoring the effect on that motivation of the results of the CD4-PE clinical trials. Applicants respectfully remind the Board that MPEP 2141 requires the examining corps to evaluate the evidence of secondary considerations of non-obviousness in every case. Applicants respectfully maintain that this required evaluation has not been made in this case.

Point 8

Point 8 does not present an argument per se but merely extends aspects of the rejections noted above to particular claims, such as those drawn to kits. Accordingly, it does not provide a separate ground of rejection and is adequately addressed by the comments made above.

III. The Rejection for Alleged Indefiniteness

Claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. According to the Action, the independent claims are

vague and indefinite by the phrase "which 3B3 Fv consists of a VH chain and a VL chain encoded by SEQ ID NO.:2". The Action maintains that it is unclear whether "both the VH and VL chains are encompassed by SEQ ID NO.:2 or both the VH and VL [chains] are individually encoded by SEQ ID NO.:2." Applicants traverse.

As an initial matter, the rejection itself is a bit unclear. It appears, however, that the concern it is trying to articulate is that the claim language could be read to mean that SEQ ID NO.:2 encodes the VH and the VL chain as a linear construct or as two separate chains. With respect, however, these alternative readings are not permissible.

The Board's attention is respectfully drawn to MPEP § 2173.02. Section 2173.02 instructs the Examining Corps that claim language "must be analyzed, not in a vacuum but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level skill in the pertinent art at the time the invention was made." (Emphasis added). Sequence listings are published with the patent specification and are part of the patent application disclosure. Persons of skill claim reviewing the sequence listing of the subject application disclosure will see the following description for SEQ ID NO.:2: "Description of Artificial Sequence: 3B3V-H(Gly-4Ser)-3V-L nucleotide sequence". See, Sequence Listing dated December 5, 2002. Accordingly, the content of the application disclosure informs the person of skill in the art that SEQ ID NO.:2 is a nucleotide sequence encoding first the 3B3 VH chain, a linker, and then the 3B3 VL chain. Any person of skill concerned about the claim language would turn to the end of the patent, see the sequence description for SEQ ID NO.:2, and immediately understand exactly what the sequence encodes. Applicants also respectfully note that the persons of skill in this art are typically Ph.D. level scientists who can be presumed to understand the straightforward description set forth in the sequence listing.

Compliance with §112, second paragraph does not require that the language set forth in a claim be either perfect or the language an Examiner would have preferred. MPEP §2173.02 directs the examining corps that claims should be allowed which "define the patentable subject matter with a reasonable degree of particularity and definiteness. Some latitude . . .

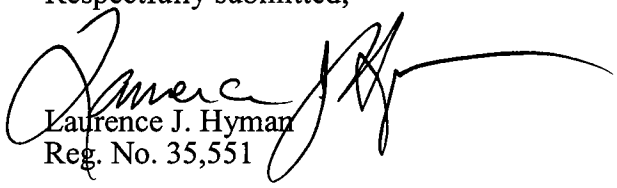
should be permitted even though the claim language is not as precise as the examiner might desire." (Emphasis in original).

In short, the alternative readings posed by the Action are not permissible in light of the application disclosure. And, even if the language of the claim is not as precise as the examiner would have liked, §112, second paragraph only requires, in the words of the MPEP, a "reasonable degree of particularity and definiteness", which is clearly met here. The Board should reverse the rejection.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,



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9. CLAIMS APPENDIX

1. (Previously presented) An immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity to the CD4 binding site of gp120 of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) and a minimum binding affinity to gp-120 of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2), wherein said immunotoxin specifically binds to and kills mammalian cells infected with HIV-1.

2. (Previously presented) The immunotoxin of claim 1, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

3. (Previously presented) The immunotoxin of claim 2, wherein said cytotoxin is a modified *Pseudomonas* exotoxin A.

4. (Previously presented) The immunotoxin of claim 3, wherein said modified *Pseudomonas* exotoxin A is selected from the group consisting of PE38, PE40, PE38KDEL (KDEL = SEQ ID NO:9), and PE38REDL (RDEL = SEQ ID NO:10).

5. (Previously presented) The immunotoxin of claim 4, wherein said modified *Pseudomonas* exotoxin A is PE38.

6. (Original) The immunotoxin of claim 1, wherein said antibody is selected from the group consisting of a single-chain Fv (scFv), a single-chain Fab (scFab), and a disulfide stabilized Fv (dsFv).

7. (Original) The immunotoxin of claim 6, wherein said antibody is a recombinantly expressed single-chain Fv.

8. Canceled

9. (Original) The immunotoxin of claim 1, wherein said immunotoxin is a fusion protein.

10. Canceled

11. (Original) The immunotoxin of claim 1, wherein said immunotoxin is suspended or dissolved in a pharmaceutically acceptable carrier or excipient.

12-18. Canceled.

19. (Withdrawn-previously presented) A single chain Fv antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

20. (Withdrawn- previously presented) The antibody of claim 19, wherein said antibody has the amino acid sequence of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) or conservative substitutions thereof.

21. (Withdrawn- previously presented) The antibody of claim 20, wherein said antibody is 3B3(Fv) Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

22. (Withdrawn- previously presented) A nucleic acid that encodes a single chain Fv antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

23. (Withdrawn- previously presented) The nucleic acid of claim 22, wherein said antibody has the amino acid sequence of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) or conservative substitutions thereof.

24. (Withdrawn- previously presented) The nucleic acid of claim 20, wherein said nucleic acid encodes the 3B3 antibody (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

25-51. Canceled.

52. (Previously presented) A kit for killing cells that display a gp120 protein, said kit comprising a container containing an immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity to the CD4 binding site of gp120 of 3B3 Fv (SEQ ID NO:1) and a minimum binding affinity to gp-120 of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2), wherein said immunotoxin specifically binds to and kills mammalian cells infected with HIV-1.

53. (Previously presented) The kit of claim 52, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

54. (Previously presented) The kit of claim 53, wherein said cytotoxin is a modified *Pseudomonas* exotoxin A.

55. (Previously presented) The kit of claim 53, wherein said immunotoxin is 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) attached to a modified *Pseudomonas* exotoxin A.

56. Canceled.

57. (Previously presented) An immunotoxin of claim 1, wherein said immunotoxin is a disulfide-stabilized ("ds") FV.

58. Canceled

59. (Withdrawn- previously presented) A nucleic acid that encodes a single chain fusion protein, said nucleic acid comprising:

(a) a nucleic acid sequence that encodes a single-chain antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded

by SEQ ID NO.:2); and

(b) a nucleic acid sequence that encodes a cytotoxin.

60. (Withdrawn- Previously presented) A nucleic acid of claim 59, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

61. (Withdrawn- Previously presented) A nucleic acid of claim 59, wherein said modified *Pseudomonas* exotoxin A is selected from the group consisting of PE38, PE40, PE38KDEL (KDEL = SEQ ID NO:9), and PE38REDL (RDEL = SEQ ID NO:10).

62. (Withdrawn- Previously presented) A nucleic acid of claim 61, wherein said modified *Pseudomonas* exotoxin A is PE38.

63. (Withdrawn) A nucleic acid of claim 59, wherein said antibody is selected from the group consisting of a single-chain Fv (scFv), a single-chain Fab (scFab), and a disulfide stabilized Fv (dsFv).

64. (Withdrawn) A nucleic acid of claim 63, wherein said antibody is a recombinantly expressed single chain Fv.

65. (Withdrawn) A nucleic acid of claim 63, wherein said antibody is a dsFv.

66-67. Canceled

68. (Previously presented) A composition, said composition comprising:
a pharmaceutically acceptable carrier or excipient; and

an immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

69. (Previously presented) A composition of claim 68, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

70. (Previously presented) A composition of claim 69, in which said modified *Pseudomonas* exotoxin A is selected from the group consisting of PE38, PE40, PE38KDEL (KDEL = SEQ ID NO:9), and PE38REDL (RDEL = SEQ ID NO:10).

71. (Previously presented) A composition of claim 70, wherein said modified *Pseudomonas* exotoxin A is PE38.

72. (Previously presented) A composition of claim 68, wherein said antibody is selected from the group consisting of a single-chain Fv (scFv), a single-chain Fab (scFab), and a disulfide stabilized Fv (dsFv).

73. (Previously presented) A composition of claim 72, wherein said antibody is a recombinantly expressed single-chain Fv.

74. (Previously presented) A composition of claim 73, wherein said antibody is 3B3(Fv) Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

75. (Previously presented) A composition of claim 72, wherein said antibody is a dsFv.

76. Canceled.

77. (Previously presented) A composition of claim 72, wherein said immunotoxin is a fusion protein.

78. Canceled.

79. (Withdrawn- previously presented) A method of killing or inhibiting the growth of a cell displaying a gp120 protein or fragment thereof, said method comprising contacting said cell with an immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

80. (Withdrawn- previously presented) A method of claim 79, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

81. (Withdrawn- previously presented) A method of claim 80, wherein said modified *Pseudomonas* exotoxin A is selected from the group consisting of PE38, PE40, PE38KDEL (KDEL = SEQ ID NO:9), and PE38REDL (RDEL = SEQ ID NO:10).

82. (Withdrawn- previously presented) A method of claim 81, wherein said modified *Pseudomonas* exotoxin A is PE38.

83. (Withdrawn) A method of claim 79, wherein said antibody is selected from the group consisting of a single-chain Fv (scFv), a single-chain Fab (scFab), and a disulfide stabilized Fv (dsFv).

84. (Withdrawn) A method of claim 83, wherein said antibody is a recombinantly expressed single-chain Fv.

85. (Withdrawn) A method of claim 83, wherein said antibody is 3B3(Fv).

86. (Withdrawn) A method of claim 83, wherein said antibody is a dsFv.

87. (Withdrawn) A method of claim 83, wherein said antibody is 3B3(dsFv).

88. (Withdrawn) A method of claim 83, wherein said immunotoxin is a fusion protein.

89. Canceled

90. (Withdrawn- previously presented) A method of killing or inhibiting the growth of cells bearing gp120 protein or fragment thereof, said method comprising administering to an organism containing said cells a composition comprising:

a pharmaceutically acceptable carrier or excipient; and

an immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) and minimum affinity of 3B3 Fv (~~SEQ ID NO:1~~ which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2).

91. (Withdrawn- previously presented) A method of claim 90, wherein said cytotoxin is selected from the group consisting of ricin, abrin, a modified diphtheria toxin, and a modified *Pseudomonas* exotoxin A.

92. (Withdrawn- previously presented) A method of claim 91, wherein said modified *Pseudomonas* exotoxin A is selected from the group consisting of PE38, PE40, PE38KDEL (KDEL = SEQ ID NO:9), and PE38REDL (RDEL = SEQ ID NO:10).

93. (Withdrawn- previously presented) A method of claim 91, wherein said modified *Pseudomonas* exotoxin A is PE38.

94. (Withdrawn) A method of claim 90, wherein said antibody is selected from the group consisting of a single-chain Fv (scFv), a single-chain Fab (scFab), and a disulfide stabilized Fv (dsFv).

95. (Withdrawn) A method of claim 94, wherein said antibody is a recombinantly expressed single-chain Fv.

96. (Withdrawn) A method of claim 94, wherein said antibody is 3B3(Fv).

97. (Withdrawn) A method of claim 94, wherein said antibody is a dsFv.

98. Canceled.

99. (Withdrawn) A method of claim 90, wherein said immunotoxin is a fusion protein.

100. Canceled.

101. (Withdrawn) A method of claim 90, further comprising administering to said organism a protease inhibitor.

102. (Withdrawn) A method of claim 90, further comprising administering to said organism a reverse transcriptase inhibitor.

103. (Withdrawn) A method of claim 90, further comprising administering to said organism both a protease inhibitor and a reverse transcriptase inhibitor and then withdrawing the reverse transcriptase inhibitor while maintaining protease inhibitor dosing during administration of said composition.

10. EVIDENCE APPENDIX

I. Evidence relied on by the Examiner with respect to the appealed grounds of rejection:

A. Matsushita et al., Aids Research Human Retroviruses 6(2):193-203 (1990)

B. Barbas, Proc Natl Acad Sci 91:3809-3813 (1994)

C. Pastan, U.S. Patent No. 5,458,878

II. Evidence relied on by Appellants, and statement of where in the record that evidence was entered by the Examiner:

A. Abstract of Ramachandran et al., J. Infect Dis 170:1009-13 (1994)

Submitted with December 9, 2003, Amendment. Considered by the Examiner in Final Action dated April 19, 2005, at page 7, in Advisory Action dated October 12, 2005, and in Office Action dated April 13, 2006, at page 6.

B. Abstract of Davey et al., J. Infect Dis 170:1180-8 (1994)

Submitted with December 9, 2003, Amendment. Considered by the Examiner in Final Action dated April 19, 2005, at page 7, in Advisory Action dated October 12, 2005, and in Office Action dated April 13, 2006, at page 6.

C. Berger, Moss and Pastan, Proc Natl Acad Sci 95:1151-11513 (1998)

Submitted with September 19, 2005 Amendment. Considered by the Examiner in Office Action dated April 13, 2006, at page 7.

D. Goldstein et al., J Infectious Diseases 181:921-6 (2000)

Submitted with December 9, 2003, Amendment. Considered by the Examiner in Final Action dated April 19, 2005, at page 7, in Office Action dated April 13, 2006 at page 6, and in Office Action dated May 3, 2007, at page 6.

E. Declaration of Dr. David J. FitzGerald.

Exhibit 1 Curriculum Vitae of Dr. David J. FitzGerald

Exhibit 2 Abstract of Chaudhary et al., Nature 335(6188):369-72 (1988)

Exhibit 3 Abstract of Berger et al., Proc Natl Acad Sci 86(23):9539-43 (1989)

Exhibit 4 Abstract of Ashorn et al., Proc Natl Acad Sci 87(220):8889-93 (1990)

Exhibit 5 Abstract of Berger et al. AIDS Res Hum Retroviruses, 6(6):795-804 (1990)

Exhibit 6 Abstract of Kennedy et al., J Leukoc Biol (epub ahead of print, printout from Pubmed dated October 8, 2006)

The Declaration and its Exhibits were submitted with the Amendment dated October 13, 2006. The Examiner noted their entry in the Office Action dated May 3, 2007, at page 2.

F. Printouts of Pubmed searches for references to anti-gp120 immunotoxins and anti-HIV immunotoxins appearing from 1990 to 1998

Submitted with Amendment dated September 19, 2005. Referred to by the Examiner in Office Action dated April 13, 2006, at pages 5-6, bridging paragraph.

11. RELATED PROCEEDINGS APPENDIX

Not applicable.